NOVARTIS

Clinical Development

OAV101/onasemnogene abeparvovec

COAV101B12302 / NCT05386680

Phase IIIb, open-label, single-arm, multi-center study to evaluate the safety, tolerability and efficacy of OAV101 administered intrathecally (1.2 x 10^{14} vector genomes) to participants 2 to <18 years of age with spinal muscular atrophy (SMA) who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®)

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment 2
Release date:	5-Dec-2024
Number of pages:	51

Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
26-Oct-2022	Prior to First Patient First Visit	Creation of final version	N/A - Final version	NA
28-Feb-2024	Post protocol amendment 1	Updated accordingly with respect to protocol amendment 1	The upper age limit has been expanded to <18 years to align with protocol amendment 1	Multiple sections
			Textual edits made to align with protocol amendment 1	Multiple sections
			[redacted]	
			Secondary estimand has been added to align with protocol amendment 1	Section 1.2.2
			Added text for handling inexact values	Section 2.1
			Risk terminology has been updated to "transient thrombocytopenia" and "new malignancies" has been added as an AESI to align with	Section 2.1.1, Section 2.7.1.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			protocol amendment 1	
			Removed text for ECG and ECHO presenting without windowing	Section 2.1.2
			[redacted]	[redacted]
			Added wording for listings for Japanese subjects	Section 2.2.1
			Added derivation for age in years at Screening Visit 1 and age in years at dosing	Section 2.3.2
			Added SMN2 copy number, number of patients with 1 vs 0 SMN1 copy number, HFMSE, RULM and ACEND at baseline	Section 2.3.2
			Updated analysis for treatment compliance	Section 2.4.1
			Updated definition for prior medication for accuracy	Section 2.4.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated analysis for prednisolone equivalent	Section 2.4.2.1
			Reworded derivation for ACEND score	Section 2.6.2
			Removed sensitivity analyses	Section 2.6.5
			Added potential sensitivity analysis for patients reinitiated SMA-disease modifying drug	Section 2.6.3 and Section 1.2.2
			Updated text to clarify summary for AEs	Section 2.7.1
			Removed text for AESIs definitions and referred them to Novartis eCRS	Section 2.7.1.1
			Added local labs as a source of laboratory data	Section 2.7.3
			Updated text for the parameters of the laboratory data, updated text for shift tables, and added >2x ULN and >8x ULN to the summary criteria	Section 2.7.3
			Updated text for ECG analysis	Section 2.7.4.1
			Removed language for ACEND box whisker plots	Section 2.10

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Removed the MMRM analysis for ACEND [redacted]	Section 2.10
			Updated text to specify clinically significant blood pressure criteria for participants with height below 5th and above 95th percentile	Section 5.6

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated text and tables for clinically significant vital signs criteria to reflect participants 18 years and above at assessments	Section 5.6
			Removed text for listings of multiple endpoints	Multiple sections
5-Dec-2024	Post protocol amendment 2	Updated the SAP to accommodate changes post dry-run	Updated baseline value for HFMSE and RULM to use the average of scores from Screening visit 1 and Baseline visit	Section 2.1.1
			Updated Week 52/EOS visit to Week 52 visit, and updated analysis window for Week 52 visit up to last participation day	Section 2.1.2
			Added ACEND total score at baseline and number of participants with hospitalizations for pneumonia in the demographics and baseline characteristics table	Section 2.3.2 and Section 2.3.3
			Provided additional details of the analysis to be performed for prednisolone or equivalent	Section 2.4.2.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated the derivation of ACEND total score and domain scores to accommodate scenarios of missing item scores and items recorded as "Not applicable"	Section 2.6.2
			Specified when more than half of participants reinitiated SMA-disease modifying drug, sensitivity analysis may be conducted for secondary endpoints	Section 1.2.2 and Section 2.6.3
			Added the listings of out of range values for chemistry and urinalysis parameters. Also, deleted the direct and indirect bilirubin parameters that were summarized in the shift tables. Additionally, updated the graphs of individual laboratory to present normalized values as multiples of ULN	Section 2.7.3
			[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	
			Added outputs required for GCP inspection by PMDA	Section 2.7.4.6
			Added the MMRM analysis for ACEND	Section 2.10
			[redacted]	[redacted]
			[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			Changed word patients to participants	Multiple sections

Table of contents

List of figures

List of tables

List of abbreviations

AAV9	Adeno-associated Virus Serotype 9
ACEND	Assessment of Caregiver Experience in Neuromuscular Disease
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
BMI	Body Mass Index
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
CE	Clinical Evaluator
[redacted]	[redacted]
CI	Confidence interval
CRF	Case Report/Record Form (paper or electronic)
CSF	Cerebrospinal fluid
[redacted]	[redacted]
CSR	Clinical Study Report
CTCAE	Common Technology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DRG	Dorsal Root Ganglia
ECG	Electrocardiogram
eCRS	electronic Case Retrieval Strategy
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in the first second
FIVC	Forced Inspiratory Vital Capacity
FVC	Forced Vital Capacity
GLDH	Glutamate Dehydrogenase
HFMSE	Hammersmith Functional Motor Scale Expanded
IT	Intrathecal
INR	International Normalized Ratio
kg	kilogram(s)
LS	Least Squares
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram(s)
[redacted]	[redacted]
mL	milliliter(s)
[redacted]	[redacted]
PT	Preferred Term
QTcF	QT interval corrected by Fridericia's formula
[redacted]	[redacted]
ROM	Range of Movement
RULM	Revised Upper Limb Module

SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMA	Spinal Muscular Atrophy
SMN	Survival of Motor Neuron
SNAP	Sensory Nerve Action Potential
SOC	System Organ Class
SOP	Standard Operating Procedure
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
vg	Vector Genome
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
[redacted]	[redacted]

1 Introduction

The purpose of this document is to provide further details about the statistical analysis methods, data derivations and data summaries for the Clinical Study Report (CSR) of study COAV101B12302: Phase IIIb, open-label, single-arm, multi-center study to evaluate the safety, tolerability and efficacy of OAV101 administered intrathecally (1.2×10^{14} vector genomes) to participants 2 to <18 years of age with spinal muscular atrophy (SMA) who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). This statistical analysis plan (SAP) has been based on International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 and E9 guidelines and in reference to protocol version 01 dated 17-May-2023. The statistical analysis plan covers statistical analysis, tabulations and listings of all data including efficacy and safety data.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified.

1.1 Study design

This is a Phase IIIb open-label, single arm, multi-center study to evaluate the safety, tolerability and efficacy of OAV101 IT in participants with SMA aged 2 to <18 years after the discontinuation of treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). Approximately 28 participants will be enrolled stratified as 2 to 5 years and 6 to <18 years with approximately 12 subjects in each stratum.

The study is comprised of 3 periods, Screening (includes Baseline), Treatment, and Follow-up.

Screening Period

Participants will undergo screening procedures for up to 45 days prior to OAV101 IT treatment during which time initial eligibility will be determined. The eligibility criterion relating to timeframe of nusinersen (Spinraza®) or risdiplam (Evrysdi®) discontinuation treatment will be confirmed at Baseline on Day -1.

On Day -1, eligible participants will be admitted to the hospital for pre-treatment Baseline procedures including prednisolone treatment (or an equivalent corticosteroid) per study protocol.

Treatment Period

On Day 1, participants meeting Screening and Baseline eligibility criteria will receive lumbar puncture with cerebrospinal fluid (CSF) withdrawal for analyses in accordance with the Assessment Schedule and receive a single IT injection of OAV101. Following OAV101 administration, participants will undergo in-patient safety monitoring over at least the next 48 hours.

Follow-up Period

During the 52-week Follow-up Period safety and efficacy assessments will be performed in accordance with the Assessment Schedule.

Final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52. At the end of study, participants will be invited to enroll in a Novartis sponsored long-term follow-up study to monitor long-term safety and efficacy.

No formal interim analysis is planned for this trial. Analyses based on ongoing data may be conducted during the trial period for internal decision-making purposes, in response to health authority requests, and/or for purposes of scientific publication.

Figure 1-1 Study design

1.2 Study objectives, endpoints and estimands

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoints(s) for primary objective(s)**
• To characterize the safety and tolerability of OAV101 IT over a 52-week period in participants with SMA aged 2 to <18 years who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®).	• Number and percentage of participants reporting adverse events (AEs), related AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs).
Secondary objective(s)	**Endpoints(s) for secondary objective(s)**
• To assess the efficacy of OAV101 IT on motor function, and caregiver impact over a 52-week period in participants with SMA aged 2 to <18 years who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®)	• Change from baseline to Week 52 visit in the HFMSE total score • Change from baseline to Week 52 visit in the RULM total Score • Change from baseline to Week 52 visit in Assessment of Caregiver Experience in ACEND instrument total score
[redacted]	

- Number and percentage of participants with suicidal ideation, suicidal behavior, or self-injurious behavior as assessed by the C-SSRS

1.2.1 Primary estimand(s)

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results.

The primary clinical question of interest is: *What is the effect on safety and tolerability of OAV101 IT for participants with SMA who were discontinued from treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®).*

The primary estimand is described by the following attributes:

1. Population: Participants with SMA aged 2 to <18 years who were treated with OAV101 IT administration after the discontinuation of nusinersen (Spinraza®) or risdiplam (Evrysdi®).
2. Endpoint (the primary variable): AEs, related AEs, SAEs and AESIs.
3. Treatment of interest: OAV101 IT

Handling of intercurrent events (including receiving prohibited concomitant medications):

Treatment policy strategy, i.e., reporting all observed AEs, related AEs, SAEs (including death) and AESIs during the trial period, will be used regardless of whether intercurrent events occurred or not. Loss to follow-up does not impact primary estimand under treatment policy strategy.

Summary measures: The number and percentage of participants reporting AEs, related AEs, SAEs and AESIs will be summarized by age strata and overall. Summaries will also be provided by MedDRA SOC and preferred term.

1.2.2 Secondary estimand(s)

The secondary clinical question of interest is: *What is the effect on efficacy of OAV101 IT for participants with SMA who were discontinued from treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®).*

The secondary estimand is described by the following attributes:

1. Population: Participants with SMA aged 2 to <18 years who were treated with OAV101 IT administration after the discontinuation of nusinersen (Spinraza®) or risdiplam (Evrysdi®).
2. Endpoint (the secondary variable): Change from baseline to Week 52 in the HFMSE total score, change from baseline to Week 52 in the RULM total score, and change from baseline to Week 52 in the ACEND instrument total score.
3. Treatment of interest: OAV101 IT

The intercurrent events will include receiving prohibited concomitant medications, study discontinuation due to any reason. All available assessments collected up to Week 52 visit / EOS visit regardless intercurrent events will be included in the analyses following a treatment policy strategy.

Summary measures: mean changes from baseline in HFMSE total score, RULM total score as well as ACEND instrument total score.

If a significant amount of participants (more than half of participants) reinitiated SMA-disease modifying drug during the trial, we may conduct a sensitivity analysis using hypothetical strategy to handle such intercurrent event.

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the primary and final analyses. Interim analyses may be conducted by Novartis for internal decision-making purposes, in response to health authority requests, and/or for purposes of scientific publication.

Analyses will be based on this document and performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC) or later.

Categorical data will be presented as frequencies and percentages. For continuous data, the number of non-missing observations, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles may also be presented. Inexact values will be handled as follows. If a laboratory value is recorded/reported as "$>X$", "$\geq X$", "$<X$", "$\leq X$", a value of X will be taken for analysis purposes. The originally recorded value will be displayed in the listing of laboratory data.

Summary tables will be presented by visit when applicable. Without further specification, all tables will be summarized by age strata and overall.

2.1.1 General definitions

Term	Definition
Investigational drug	OAV101 ($1.2x10^{14}$vector genomes)
Date of administration of investigational drug	Date of OAV101 administration
Study day	Study day 1 is the date of the administration of investigational drug. The study day for all assessments will be calculated as follows: 1. If date of assessment occurred on or after the date of administration of investigational drug, then Study day = Date of assessment – Date of administration of investigational drug + 1. 2. If date of assessment occurred before the date of administration of investigational drug, then Study day = Date of assessment - Date of administration of investigational drug. The study day will be displayed in the data listings. Study days before the administration of investigational drug will be negative.
Baseline	• HFMSE and RULM: Baseline value for HFSME and RULM total score is defined as the average of screening 1 and baseline score, assuming that both assessments have complete and valid total scores available. If just one of the assessments collected at these two visits has a

	complete and valid total score available, then the baseline total score is defined as the single total score available. • Other assessments: The latest non-missing measurement or evaluation made prior to the administration of study treatment. If participants have no value as defined above, the baseline result will be missing.
Change from baseline	Change from baseline is defined as post-baseline value minus baseline value
Last participation day	Last participation day can be calculated using end of participation date – date of administration of investigational drug + 1
Last contact	Last contact refers to the last study visit. If the participant does not terminate the study early, it is the End of Study visit
Adverse Event (AE)	An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.
Related AE	A related AE is an AE that has at least a reasonable possibility of being causally associated with the use of a medicinal (investigational) product.

Serious Adverse Event (SAE)	An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical condition(s) which meets any one of the following criteria:
	• fatal
	• life-threatening
	• results in persistent or significant disability/incapacity
	• constitutes a congenital anomaly/birth defect
	• requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
	  • routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
	  • elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
	  • social reasons and respite care in the absence of any deterioration in the participant's general condition
	  • treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
	• is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

AE of Special Interest (AESI)	On the basis of important identified and potential risks associated with OAV101, AESIs are determined and categorized as follows. These will be summarized based using Standardized MedDRA terminology: • Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy • Cardiac adverse events • Dorsal root ganglia toxicity • New malignancies
Treatment-emergent AE (TEAE)	A Treatment-emergent AE is any AE whose onset or worsening occurred after dosing on Day 1. All AEs in the analyses are referred to TEAE by default without further notification.

2.1.2 Analysis Visit Windows

Unless otherwise specified, analysis visit windows for efficacy and safety assessments which are summarized on a by-visit basis are defined based on study day post dosing. For by-visit endpoints, the time windows describe how data will be assigned to protocol-specified time points during follow up.

The analysis windows for respective assessments are as follows:

Vital Signs, Body Weight and Neurological Examination:

Visit	Nominal days (Study Day)	Start day	End day
Day 1	Day 1	Day 1	Day 1
Day 2	Day 2	Day 2	Day 2
Day 3	Day 3	Day 3	Day 3
Week 1	Day 8	Day 4	Day 11
Week 2	Day 15	Day 12	Day 18
Week 3	Day 22	Day 19	Day 25
Week 4	Day 29	Day 26	Day 36
Week 6	Day 43	Day 37	Day 50
Week 8	Day 57	Day 51	Day 64
Week 10	Day 71	Day 65	Day 78
Week 12	Day 85	Day 79	Day 120
Week 22	Day 155	Day 121	Day 190
Week 32	Day 225	Day 191	Day 260
Week 42	Day 295	Day 261	Day 330
Week 52	Day 365	Day 331	Last participation day

C-SSRS, Clinical Chemistry and Medical Resource Utilization:

Visit	Nominal days (Study Day)	Start day	End day
Week 1	Day 8	Day 1	Day 11
Week 2	Day 15	Day 12	Day 18
Week 3	Day 22	Day 19	Day 25
Week 4	Day 29	Day 26	Day 36
Week 6	Day 43	Day 37	Day 50
Week 8	Day 57	Day 51	Day 64
Week 10	Day 71	Day 65	Day 78
Week 12	Day 85	Day 79	Day 120

Week 22	Day 155	Day 121	Day 190
Week 32	Day 225	Day 191	Day 260
Week 42	Day 295	Day 261	Day 330
Week 52	Day 365	Day 331	Last participation day

Hematology:

Visit	Nominal days (Study Day)	Start day	End day
Day 2	Day 2	Day 1	Day 2
Week 1	Day 8	Day 3	Day 11
Week 2	Day 15	Day 12	Day 18
Week 3	Day 22	Day 19	Day 25
Week 4	Day 29	Day 26	Day 36
Week 6	Day 43	Day 37	Day 50
Week 8	Day 57	Day 51	Day 64
Week 10	Day 71	Day 65	Day 78
Week 12	Day 85	Day 79	Day 120
Week 22	Day 155	Day 121	Day 190
Week 32	Day 225	Day 191	Day 260
Week 42	Day 295	Day 261	Day 330
Week 52	Day 365	Day 331	Last participation day

HFMSE, RULM, ACEND, [redacted]

Visit	Nominal days (Study Day)	Start day	End day
Week 4	Day 29	Day 1	Day 43
Week 8	Day 57	Day 44	Day 71
Week 12	Day 85	Day 72	Day 120
Week 22	Day 155	Day 121	Day 190
Week 32	Day 225	Day 191	Day 260
Week 42	Day 295	Day 261	Day 330
Week 52	Day 365	Day 331	Last participation day

Body Height, BMI, [redacted]

Visit	Nominal days (Study Day)	Start day	End day
Week 4	Day 29	Day 1	Day 43

Week 8	Day 57	Day 44	Day 106
Week 22	Day 155	Day 107	Day 190
Week 32	Day 225	Day 191	Day 260
Week 42	Day 295	Day 261	Day 330
Week 52	Day 365	Day 331	Last participation day

[redacted]

Echocardiogram and ECG:

Visit	Nominal days (Study Day)	Start day	End day
Week 1	Day 8	Day 1	Day 18
Week 4	Day 29	Day 19	Day 43
Week 8	Day 57	Day 44	Day 106
Week 22	Day 155	Day 107	Day 260
Week 52	Day 365	Day 261	Last participation day

[redacted]

[redacted], pulmonary function testing, [redacted]

Visit	Nominal days (Study Day)	Start day	End day
Week 4	Day 29	Day 1	Day 43
Week 8	Day 57	Day 44	Day 106
Week 22	Day 155	Day 107	Day 225
Week 42	Day 295	Day 226	Day 330
Week 52	Day 365	Day 331	Last participation day

Troponin I:

Visit	Nominal days (Study Day)	Start day	End day
Week 1	Day 8	Day 1	Day 18
Week 4	Day 29	Day 19	Day 43
Week 8	Day 57	Day 44	Day 71
Week 12	Day 85	Day 72	Day 225
Week 52	Day 365	Day 226	Last participation day

If more than one observation is included in a time window for HFMSE, RULM [redacted] irrespective of the observations being scheduled or unscheduled, the latest observation will be used in analyses.

For other endpoints, when an assessment value for both a scheduled visit and an unscheduled visit are present within the same analysis window, the scheduled visit value will be used. Unscheduled visit data will only be used when there is no measurement from the scheduled visit in the defined window.

If more than one scheduled observation for a specific assessment is included in a time window, the assessment closer to the nominal time will be used. If there are two scheduled observations equally distant to the nominal time, the latest one will be used in analyses.

[redacted]

2.2 Analysis sets

The full analysis set (FAS) is comprised of all participants who are enrolled in this study and received OAV101 through IT administration. The safety analysis set (SAF) is defined as the same as the FAS, therefore all the efficacy and safety analyses will be conducted using FAS.

2.2.1 Subgroup of interest

Age at the time of informed consent, grouped as 2 to 5 years (inclusive of all 5-year-olds) and 6 to <18 years, is considered to be the subgroup of interest for this SAP.

In addition, key safety and efficacy data for Japanese subjects only will also be analyzed according to Japanese health authority requirement.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Disposition will be presented by age strata and overall for all participants, and will include the following summaries:

- Number of participants screened will be presented.
- Number and percentage of screened participants who subsequently failed screening, along with the reasons for screen failure will be summarized. A listing of screened participants who are not treated with reasons for screen failure will be produced as well.
- Number and percentage of participants in FAS who completed the study, and prematurely discontinued the study as of the time of reporting will be summarized. Among those who prematurely discontinued the study, the distribution of primary reasons for discontinuation will be enumerated.

A listing of participant disposition in FAS will be produced.

2.3.2 Demographics and other baseline characteristics

The age of the participant at the time of the Screening Visit 1 and age at dosing will be summarized using descriptive statistics. The participant's age will be collected on the CRF in terms of both years and months (i.e. a participant's age may be recorded as 5 years, 2 months old). Age in years will be derived for each participant as follows:

- Age at Screening Visit 1 (days) = (recorded years *365.25) + (recorded months*30.4375)
- Age at Screening Visit 1 (years) = Age at Screening Visit 1 (days)/365.25
- Age at dosing (years) = (Treatment start date - Screening visit 1 date + age at Screening visit 1 in days)/365.25

The following demographic and baseline characteristics will be summarized by age strata and overall for the FAS:

- Age at Screening Visit 1(years)
- Age at dosing (years)
- Sex
- Race
- Ethnicity
- Country
- Weight (kg)

- Height/length (cm)
- BMI
- SMN2 copy number (study specific genetic reconfirmation)
- Number of participants with 1 vs 0 SMN1 copy number
- HFMSE total score at baseline
- RULM total score at baseline
- ACEND domain 1 total score at baseline
- ACEND domain 2 total score at baseline
- ACEND total score at baseline

If a participant reports multiple races, they will be categorized as "multiple races" in the summary table.

Confirmatory genetic testing will be listed for the FAS.

2.3.3 Medical history

The presence of significant medical conditions obtained at study entry and occurred prior to informed consent will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The dictionary version used will be noted in the summary tables and listings. Summaries will be produced by age strata and overall for the FAS.

The following parameters will be summarized regarding symptoms and history of SMA:

- Previous SMA diagnosis method (e.g., prenatal genetic testing, genetic new born screening, genetic testing based on symptoms, clinically diagnosed with no genetic testing)
- Type of *SMN1* pathogenic variants on each allele (e.g., deletion, point mutation)
- Positive for *SMN2* gene modifier G>C.859
- *SMN2* gene copy number
- Age at SMA symptom onset
- Age at previous SMA diagnosis
- Highest motor function achieved
- Type and frequency of physical therapy
- Number of participants with hospitalizations for pneumonia with or without respiratory failure
- Number of hospitalizations for pneumonia with or without respiratory failure

- Familial history of SMA, including parent carriers and affected sibling(s)
- Prior SMA treatment, duration of treatment, and reason for discontinuation
- SMA symptoms ongoing on Screening Visit 1 and SMA symptoms experienced in the past

Age at previous SMA diagnosis will be derived for each participant as follows:

- Age at Screening visit 1 (days) = (recorded years *365.25) + (recorded months*30.4375)
- Age at previous SMA diagnosis (years) = (previous SMA diagnosis date - Screening visit 1 date + age at Screening visit 1 in days)/365.25

Symptoms and history of SMA will be summarized by age strata and overall for the FAS.

SMA medical history and diagnosis will be listed.

2.3.4 Protocol deviations

All important protocol deviations (PDs) will be recorded in the clinical database and will be categorized in accordance with Novartis SOPs. PDs through the end of study will be summarized by PD coded term for each age stratum and overall for FAS. A listing of all important PDs occurring through the end of the study will also be created.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The following details pertaining to treatment administration will be summarized using descriptive statistics by age strata and overall for FAS:

- Anatomical location of administration (L2-L3, L3-L4, L4-L5, L5-S1)
- Total volume administered
- Number and percentage of participants with dose interruption and their corresponding reason
- Treatment compliance (%) if the dose is not fully completed. Treatment compliance is defined as 100 times the dose administered divided by the planned dose. Planned dose is 3 ml, equivalent to 1.2×10^{14} vector genomes.

A listing of treatment administration will be produced.

2.4.2 Prior and concomitant therapies

Prior and concomitant medications and significant non-drug therapies taken prior to and after the start of the study treatment will be listed and summarized according to the World Health Organization (WHO) Drug Dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system. The dictionary version used will be noted in the summary tables and listings.

A prior medication or significant non-drug therapy is defined as any medication or significant non-drug therapy taken prior to the date of the administration of investigational drug. A concomitant medication or significant non-drug therapy is defined as any medication or significant non-drug therapy that started prior to the date of the administration of investigational drug and continued to be taken after the administration of investigational drug or any medication or significant non-drug therapy that started on or after the date of the administration of investigational drug.

The number and percentage of participants in the FAS taking prior medications and significant non-drug therapies and concomitant medications and significant non-drug therapies through the end of study will be summarized by ATC, generic drug name based on the WHO Drug Dictionary, age strata and overall.

Listings will be produced to summarize the prior and concomitant medications taken throughout the study. A listing of previous SMA-disease modifying treatment will also be produced.

2.4.2.1 Specific medication subgroups

To mitigate safety risks associated with immune response to the AAV9 capsid that may occur after administration of OAV101, all participants will receive immunomodulatory therapy with prednisolone or equivalent. Starting approximately 24 hours prior to OAV101 IT injection, prednisolone or equivalent will be instituted according to the schedule in Table 6-2 in protocol.

The total number of days receiving prednisolone or equivalent, total cumulative dose of prednisolone administered through the study (mg/kg) and dose intensity (mg/kg/day), derived from the prednisolone log, will be computed for each participant, and summarized by age strata and overall. [redacted] In cases when other glucocorticosteroids were used, the doses will be converted into prednisolone equivalent doses according to the relative potency, for example with a factor of 0.25 for hydrocortisone, 6.67 for dexamethasone and 1.25 for methylprednisolone. The number and percentage of participants with prednisolone equivalent dose will also be presented per corticosteroid type, age strata and overall.

To compute total cumulative dose, the total dosing period is subdivided into dosing intervals represented by constant dose levels. Total doses per dose level and dosing interval are derived as the product of dose level in mg/kg and the number of days of the dosing interval. For the total cumulative dose, all products per dose level and dosing interval are summed up.

Prednisolone or equivalent exposure will be summarized and listed for the FAS.

2.5 Analysis supporting primary objective(s)

A final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52.

2.5.1 Primary endpoint(s)

The primary endpoint of the study is the number and percentage of participants reporting AEs, related AEs, SAEs, and AESIs. For details, see Section 2.7.

2.5.2 Statistical hypothesis, model, and method of analysis

The number and percentage of participants reporting AEs, related AEs, SAEs, and AESIs will be summarized by age strata and overall in the FAS. Summaries will also be provided by MedDRA system organ class and preferred terms.

No hypothesis testing will be performed.

2.5.3 Handling of intercurrent events

All intercurrent events including receiving prohibited concomitant medications will be handled by treatment policy strategy, namely, all AEs, related AEs, SAEs (including death), and AESIs observed while/after receiving prohibited concomitant medications will be reported.

2.5.4 Handling of missing values not related to intercurrent event

Not applicable.

2.5.5 Sensitivity analyses

Given the descriptive nature of the summary of primary safety endpoints, no sensitivity analyses will be performed.

2.5.6 Supplementary analyses

No supplementary analysis will be performed.

2.6 Analysis supporting secondary objectives

A final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52.

2.6.1 Secondary endpoint(s)

The secondary endpoints of the study are:

1. Change from baseline to Week 52 visit in the HFMSE total score
2. Change from baseline to Week 52 visit in the RULM total score
3. Change from baseline to Week 52 visit in Assessment of Caregiver Experience in ACEND instrument total score

2.6.2 Statistical hypothesis, model, and method of analysis

Change from baseline to Week 52 visit in the HFMSE total score, the RULM total score and the ACEND instrument total score will be summarized descriptively by age strata and overall for the FAS based on observed cases.

No hypothesis testing will be performed.

HFMSE was devised for use in children with SMA Type 2 and Type 3 to give objective information on motor ability and clinical progression (Glanzman et al 2011) and has been used in a double blinded clinical trial of Type 2 SMA to demonstrate efficacy of SMN-targeting therapy (Mercuri et al 2012). HFMSE is a SMA-specific 33-item assessment that is administered by clinical evaluators in a short period of time, requires minimal equipment, and is designed to factor in participant fatigue. Each motor skill item is scored on a 3-point Likert scale from 0 (no response) to 2 (full response), with a total score range of 0 to 66. A higher score indicates a higher ability level. A total score will not be derived if any item score is missing or "cannot test".

HFMSE assessment will be administered by a qualified site clinical evaluator (CE) in accordance with the Assessment Schedule for all participants.

RULM is a validated, SMA-specific assessment that measures motor performance in the upper limbs from childhood through adulthood in ambulatory and never ambulatory individuals with SMA, and weaker individuals who have a floor effect or very low score on the Hammersmith Functional Motor Scale (HFMS) (Mazzone et al 2017). The revised version of the test consists of 19 scorable items: 18 items scored on a 0 (unable) to 2 (full achievement) scale and one item that is scored from 0 (unable) to 1 (able). These item scores are summed to give a total score ranging from 0 to 37 points with higher scores reflecting higher ability. RULM consists of upper limb performance items that are reflective of reachable space and activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, and remove the lid of a container). A total score will not be derived if any item score is missing or "cannot test".

RULM will be administered by a qualified site clinical evaluator (CE) in accordance with the Assessment Schedule for all participants starting at 30 months of age.

ACEND instrument has been designed to quantify the caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA (Matsumoto et al 2011). ACEND instrument includes two domains and a total of seven subdomains assessing physical impact (i.e., Domain 1, including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (i.e, Domain 2, including time, emotion, and finance); each subdomain comprises several items. Total scores for subdomains are standardized to range from 0 to 100 by means of 100 x (average of applicable non-missing raw item scores – 1) / (maximum item score – 1). Domain 1 and Domain 2 scores are calculated as average of the subdomain scores for each domain. Total score is calculated as average of all the 7 subdomain scores. Higher scores indicate a better caregiver experience. Items scored as "Not Applicable" will be considered as missing. At least half of the items in the corresponding subdomains need to be non-missing for a subdomain score to be calculated, and at least half of the corresponding subdomains need to be non-missing for Domain 1 or Domain 2 scores to be calculated. Total score will be calculated when both Domain 1 and Domain 2 scores are non-missing.

The primary parent/caregiver of participants will complete the ACEND instrument according to the Assessment Schedule.

2.6.3 Handling of intercurrent events

The analyses will account for intercurrent events as follows:

1. **Use of prohibited concomitant medications:** Assessments collected while/after receiving prohibited concomitant medications will be included in the analyses (following a treatment policy strategy as in the primary estimand).
2. **Study discontinuation due to any reasons:** change from baseline to Week 52 visit in the HFMSE total score, the RULM total score and the ACEND instrument total score will be summarized for all data available.

If a significant amount of participants (more than half of participants) reinitiated SMA-disease modifying drug during the trial, we may conduct a sensitivity analysis using hypothetical strategy to handle such intercurrent event.

2.6.4 Handling of missing values not related to intercurrent event

Missing values not related to intercurrent events, e.g., total score can not be derived due to "cannot test" in HFMSE or RULM items, will not be imputed.

2.6.5 Sensitivity analyses

No sensitivity analysis will be performed.

2.6.6 Supplementary analyses

No supplementary analysis will be performed.

2.7 Safety analyses

Safety will be assessed through physical and neurological examinations, sensory nerve action potentials (SNAPs), magnetic resonance imaging (MRI), vital signs, height and weight measurements, 12-lead ECGs, echocardiograms, laboratory assessments, suicidal ideation and behavior, use of concomitant medications and AE monitoring. AE will be coded in accordance with the most current version of the MedDRA coding dictionary. The actual version of the MedDRA coding dictionary used will be noted in the summary tables and in the clinical study report. All safety data will be based on the FAS and will be summarized by age strata and overall.

2.7.1 Adverse events (AEs)

Summary tables of AEs reported through the study will be presented, consisting of the number and percentage of participants experiencing at least one event for each of the following categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to the study treatment
- Any treatment-emergent SAE

- Any treatment-emergent SAE related to the study treatment
- Any severe treatment-emergent AE
- Any treatment-emergent AEs leading to discontinuation from study
- Any treatment-emergent AEs leading to death
- Any treatment-emergent AESI

The number and percentage of participants with treatment-emergent AEs will be summarized along with the total number of unique events in the following ways:

- By age strata, and PT
- By age strata, primary SOC, and PT
- By age strata, primary SOC, PT, and maximum severity for treatment-emergent AE
- AESI will be summarized by age strata, AESI category, maximum severity, and PT

All information obtained on AEs (including those reported during screening period) through the end of study will be listed by age strata and participant.

The following summaries will also be generated by SOC and PT:

- Any non-serious treatment-emergent AE reported in >5% of participants
- Any treatment emergent serious adverse events and SAE suspected to be related to study treatment

If for a same participant, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

SOCs will be presented in alphabetical order and the PTs will be presented by descending number of participants with events by overall column within each SOC.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block, e.g., among AE's in ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number SAEs leading to deaths will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest / grouping of AEs

On the basis of important identified and potential risks associated with OAV101, AESIs are determined and categorized as follows. These will be summarized based using Standardized MedDRA terminology:

- Hepatotoxicity

- Transient thrombocytopenia
- Thrombotic microangiopathy
- Cardiac adverse events
- Dorsal root ganglia toxicity
- New malignancies

AESIs will be identified using Novartis eCRS.

Thrombotic microangiopathy will be identified via the following PTs: thrombotic microangiopathy OR haemolytic uraemic syndrome OR atypical haemolytic uraemic syndrome.

All AESIs will be listed by risk name.

2.7.2 Deaths

Deaths will be presented in both a data listing and a summary table for AEs with fatal outcome, including cause of death and other details such as autopsy if given. All data will be considered for analysis up to the time of death.

2.7.3 Laboratory data

Safety laboratory data and genetic diagnosis laboratory data analyzed by the central laboratory as well as by local labs will be used in all analyses. The FAS will be used for all summaries of data.

Values at each scheduled visit as well as change from baseline values to each post-baseline visit through the end of study will be summarized for each protocol-specified laboratory values (hematology, chemistry including liver function test and troponin I) using descriptive statistics. Listing of platelet and abnormal values for other hematology parameters, out of range values for chemistry parameters and out of range values for urinalysis parameters will also be produced. For each applicable time point, only participants with a measurement for that time point will be included in the summary.

In addition, shift tables based on CTC grade (CTCAE version 5) will be provided for all laboratory parameters that were defined in the Novartis Internal Guidance on CTCR Grading of Lab Parameter (e.g., platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase, and serum total bilirubin, etc. Activated partial thromboplastin time, prothrombin time, and international Normalized Ratio will not be displayed in shift table.) to compare a participant's baseline laboratory evaluation relative to the post-baseline values. For laboratory (serum) parameters Glutamate Dehydrogenase and Troponin I, shift tables will be produced by below, within, or above the normal range level based on normal ranges of the laboratory used in this study (Low/Normal/High).

The shift tables will cross tabulate the frequency (number and percentage) of participants with baseline versus post-baseline level. These summaries will be presented by laboratory test and treatment group for each age strata and overall. The shift tables will present shifts from baseline

to each visit and to final value. Moreover, for laboratory parameters based on CTC grade, shift tables from baseline to the worst CTC grade level at any time post-baseline will be generated. Participants with specific laboratory abnormalities (defined by CTC grade 3 and 4) will be listed. For laboratory parameters based on Low/Normal/High range, shift tables from baseline to the maximum at any time post-baseline will be generated.

Normalized values (absolute values/ULN) as well as change from baseline in absolute values of ALT, AST, ALP, total bilirubin and troponin-I over time will be visualized by individual longitudinal trajectories. Absolute values as well as change from baseline in absolute values of platelets will also be visualized by individual longitudinal trajectories.

The number and percentage of participants meeting each of the following criteria through the end of study will be summarized by age strata and overall:

Peak post-baseline values:

- ALT >2x ULN, ALT >3x ULN, ALT >5x ULN, ALT >8x ULN, ALT >10x ULN, ALT >20x ULN
- AST >2x ULN, AST >3x ULN, AST >5x ULN, AST >8x ULN, AST >10x ULN, AST >20x ULN
- ALT or AST >2x ULN, ALT or AST >3x ULN, ALT or AST >5x ULN, ALT or AST >8x ULN, ALT or AST >10x ULN, ALT or AST >20x ULN
- Total bilirubin >1.5x ULN, Total bilirubin >2x ULN, Total bilirubin >3x ULN

Combined elevations post-baseline:

- ALT or AST >3x ULN and Total bilirubin >2x ULN
- ALT or AST >3x ULN and Total bilirubin >2x ULN and ALP ≥2x ULN
- ALT or AST >3x ULN and Total bilirubin >2x ULN and ALP <2x ULN

For the last three combination categories, the values do not need to have been collected at the same assessment.

For participants meeting any elevation criterion, a corresponding listing of all ALT, AST, alkaline phosphatase, INR, GLDH, and total, direct, and indirect bilirubin values will be provided.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

A 12-lead ECG and standard transthoracic ECHO will be conducted at the scheduled visits in accordance with the Schedule of Study Assessments. ECGs and ECHOs will be interpreted locally by a cardiologist or a designee for immediate safety evaluation. The ECG tracings or ECG machine data and ECHOs will also be collected for centralized review and will have a central interpretation available (without assessment of clinical significance). ECHOs will also undergo interpretation by a cardiologist. For continuous ECG parameters, the mean value for

each visit will be calculated from the triplicate ECGs for each participant. For categorical ECG parameters, the worst value from the triplicate ECGs for each visit will be used for each participant. The FAS will be used for all summaries of data.

For 12-lead ECG, observed values as well as change from baseline values will be summarized at each scheduled visit through the end of the study using descriptive statistics for the following parameters as measured by the central reviewer: RR, PR, QRS, QT, and QT interval corrected by Fridericia's formula (QTcF). Additionally, a summary of ECG interpretation (normal, abnormal) at each scheduled visit through the end of the study will be provided and a summary (number and percentage) of participants meeting the following criteria at anytime post baseline will be provided.

- New maximum QTcF value: > 450 msec to ≤ 480 msec, > 480 msec to ≤ 500 msec and > 500 msec. For criteria based on only absolute values, participants must have post baseline value for that parameter and missing baseline or baseline value not meeting the criteria as below.
  - New > 450 to ≤ 480 msec means baseline ≤ 450.
  - New > 480 to ≤ 500 msec means baseline ≤ 480.
  - New > 500 msec means baseline ≤ 500.
- Maximum increase from baseline in QTcF: > 30 msec to ≤ 60 msec, > 60 msec.

For ECHO, the following data will be summarized by age strata, considering post-baseline data through the end of study:

- Number and percentage of participants with intracardiac thrombi
- Number and percentage of participants with low cardiac function

These parameters are defined as follows:

Intracardiac thrombi: Post-baseline ECHO result of Thrombus present (response of Yes).

Low cardiac function: Post-baseline ECHO results of Left Ventricular Ejection Fraction (LVEF) <56% or Left Ventricular Fractional Shortening (LVFS) <28%.

2.7.4.2 Vital signs

Vital signs will be assessed at the scheduled visits in accordance with the Schedule of Study Assessments. All summaries of data will be based on the FAS.

Observed values as well as change from baseline values will be summarized at each scheduled visit through the end of study using descriptive statistics for systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, pulse, and pulse oximetry.

Vital sign results will be flagged as clinically significant if they meet the pre-specified criteria which are defined in Appendix 5.6. The number and percentage of participants meeting each clinically significant criterion through the end of study will be summarized. A listing of all clinically significant vital sign values will also be produced.

2.7.4.3 Anthropometry

Anthropometry will be assessed at the scheduled visits in accordance with the Schedule of Study Assessments. All data will be summarized using the FAS.

Observed values as well as change from baseline values through the end of study will be summarized at each scheduled visit for body height as derived from tibial length, weight, and BMI.

The following equation will be used for both males and females to estimate height in males and females who are ≥ 2 to ≤ 12 years of age (Stevenson Equation).

- Height = (3.26 × TL) + 30.8
- TL=Tibial length

The following equations will be used for males and females to estimate height in males and females who are > 12 years of age (Gauld Equation).

- Males: Height = (2.758 × TL) + (1.717 × A) + 21.818
- Females: Height = (2.771 × TL) + (1.457 × A) + 37.748
- TL = Tibial length (cm)
- A = age in years to one decimal place

The following equation will be used for BMI calculation:

- $BMI = W / H^2$
- W = weight in kilograms (kg) to two decimal places
- H = height in meters (m) to two decimal places

2.7.4.4 Neurological examination and Sensory Nerve Action Potential

The incidence of abnormal findings occurring post-baseline and through the end of study resulting from the neurological examination of proprioceptive, vibratory, tactile and pain sensation will be summarized by age strata and overall using the FAS.

A listing of neurological examination data collected through the end of study will also be produced.

To complement neurological examination in case of sensory abnormalities, radial and sural nerve sensory nerve action potential (SNAP) will be assessed. SNAP parameters consist of the overall interpretation (present, absent, unable to obtain) for both the right and left limbs. These data collected at Screening will be summarized by age strata and overall using the FAS. Post-treatment, SNAP will be performed if there are sensory abnormalities in the neurological examination.

A listing of all SNAP data collected through the end of study will also be produced.

2.7.4.5 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and behavior (SIB). It will be assessed at the scheduled visits in accordance with the Schedule of Study Assessments and at all unscheduled visits. There are two versions of the questionnaire:

- The "baseline/screening" version, which is to be performed at the first visit. It assesses SIB during the subject's lifetime, and
- The "since last visit" version to be used at subsequent visits, assessing SIB since last visit.

The 11 preferred SIB categories described in table below, corresponding to the expanded C-CASA categories (Columbia Classification Algorithm for Suicide Assessment), have been adopted as standard by FDA to report SIB ([Food and Drug Administration Guidance for Industry, 2012], [Nilsson et al, 2013]). These categories include five levels of suicidal ideation, five levels of suicidal behavior and the category self-injurious behavior, no suicidal intent. Each category has a binary response (yes/no). The C-SSRS questionnaire allows suicidal ideation and behavior to be classified into these 11 preferred categories.

Table 2-1 Standard SIB events

Category number	C-SSRS category
Suicidal Ideation	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal behavior	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt
Completed suicide	
Self-injurious behavior without suicidal intent	

Self-injurious behavior without suicidal intent is defined as an event in the category 'non-suicidal self-injurious behavior'.

SIB assessments obtained before the treatment of study drug will be defined as *all prior history* which is the SIB results obtained from the *lifetime* assessment.

SIB data will be summarized descriptively by age strata and overall using the FAS. The number and percentage of subjects reporting suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior without suicidal intent will be presented by analysis-

period (all prior history and any time post-baseline). Because the C-SSRS is only administered in participants >7 years of age, percentages will be based on the number of participants who were assessed, rather than the total number of participants in the FAS.

Any suicidal ideation or behavior (a 'yes' answer to at least one of the categories 1-10 suicidal ideation and behavior questions in analysis-period of interest) will be summarized.

In addition, the number and percentage of subjects with the following post-baseline events will be presented:

- Emergence of suicidal behavior compared to all prior history: The occurrence of suicidal behavior (Categories 6-10) at any time post-baseline from not having suicidal behavior (Categories 6-10) prior to treatment.

2.7.4.6 Outputs required for GCP inspection by PMDA

The date of the first subject first visit and the date of the last subject last visit will be presented by country and center. In addition, the number of subjects with informed consent signed, treated, discontinued from the study and with AEs suspected to be related to study treatment will be summarized by country and center.

2.8 Pharmacokinetic endpoints

Not applicable

2.9 PD and PK/PD analyses

Not applicable

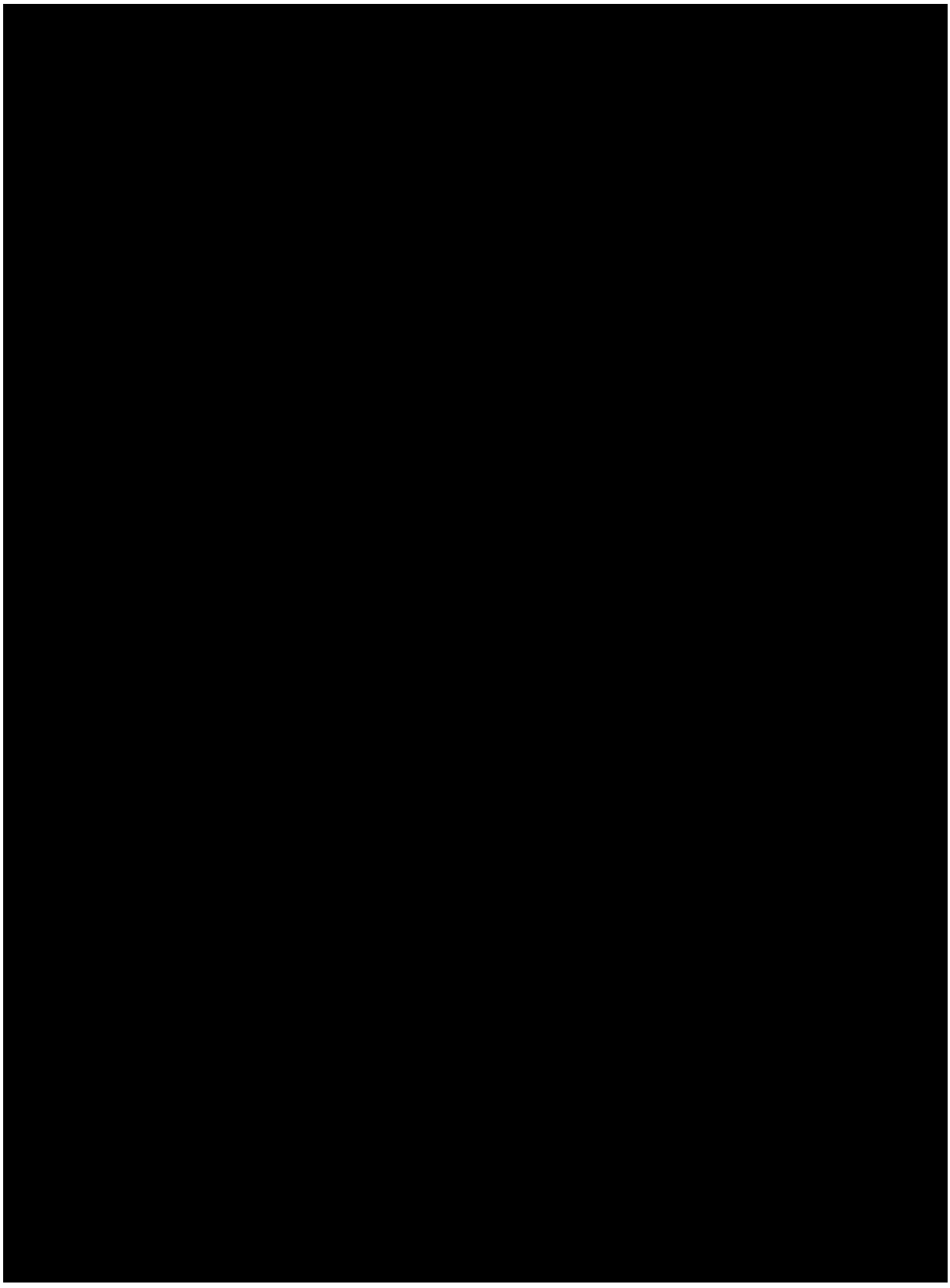
2.10 Observer-reported outcomes

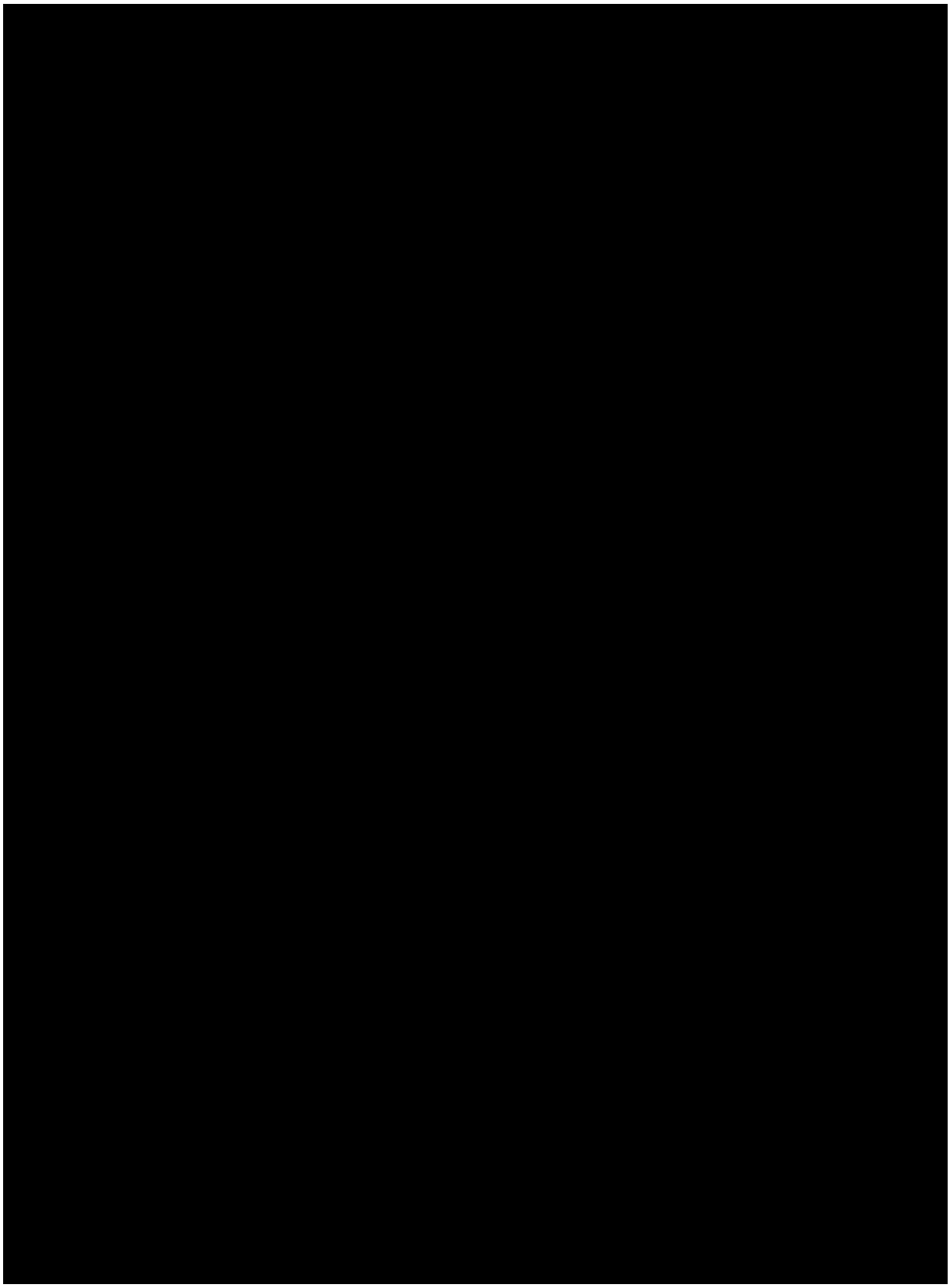
The ACEND instrument is an observer-reported outcome that will be summarized descriptively by age strata and overall for the FAS.

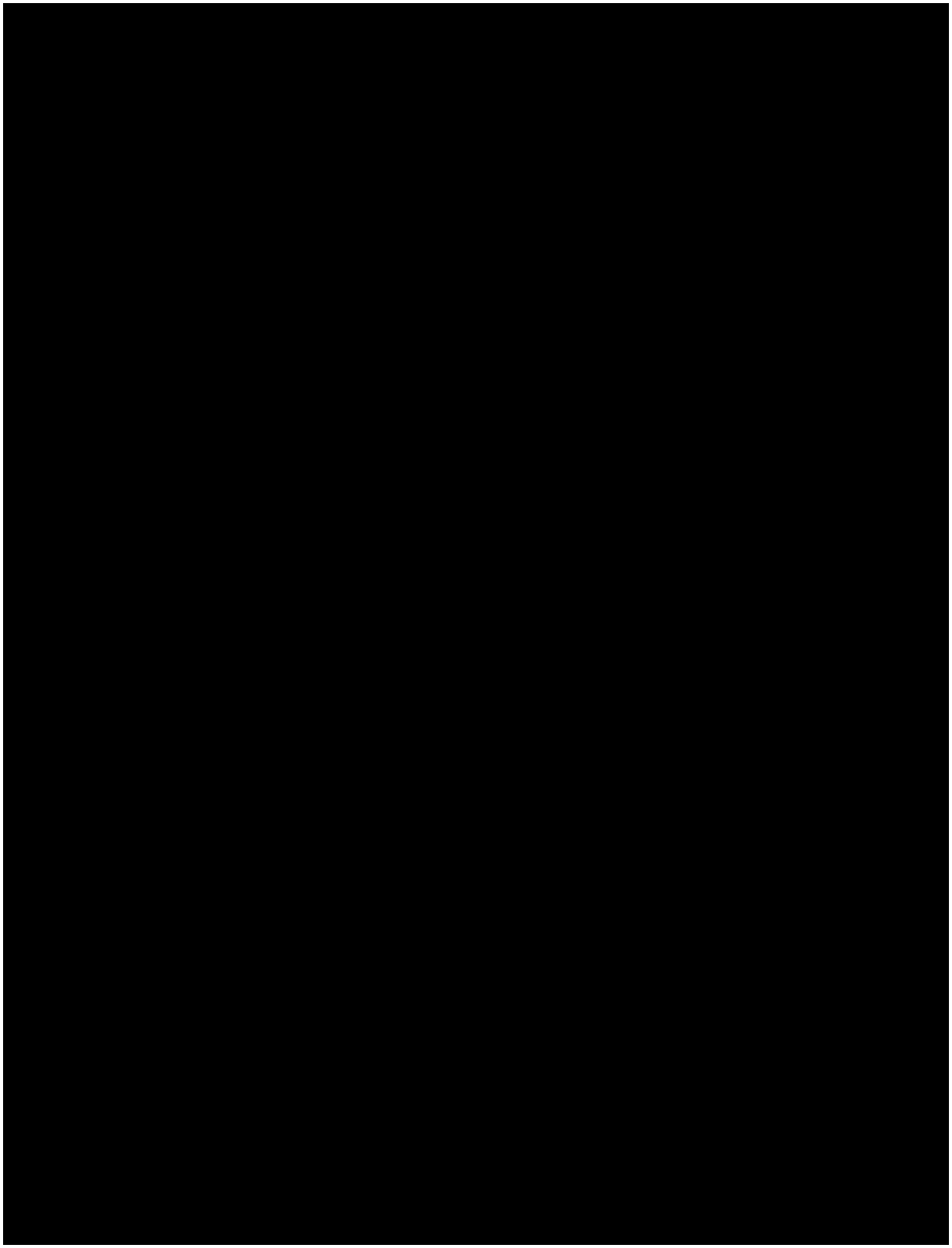
Change from baseline in the ACEND instrument total score, total domain scores and subdomain scores will be summarized descriptively for each scheduled visit by age strata and overall based on observed cases. ACEND total score, total domain scores, changes in ACEND total score and changes in total domain scores will be visualized by individual longitudinal trajectories.

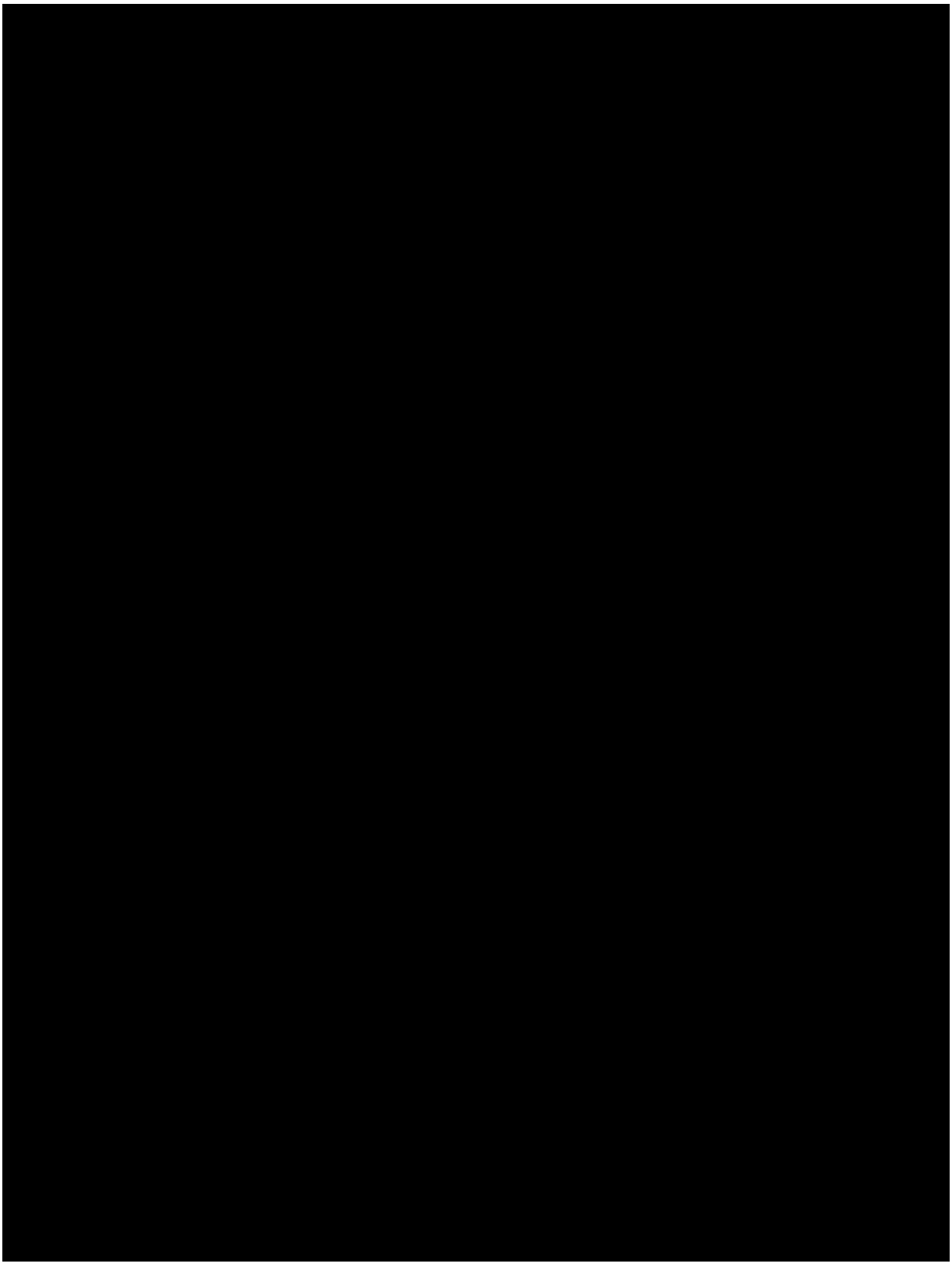
In addition, mixed models with repeated measurement analysis will be performed for ACEND total score as well based on all observed data with fixed factors including age stratum at baseline, visit and baseline ACEND total score. An unstructured covariance matrix will be used. The LS means, standard errors, and 95% 2-sided confidence intervals will be reported for each scheduled visit.

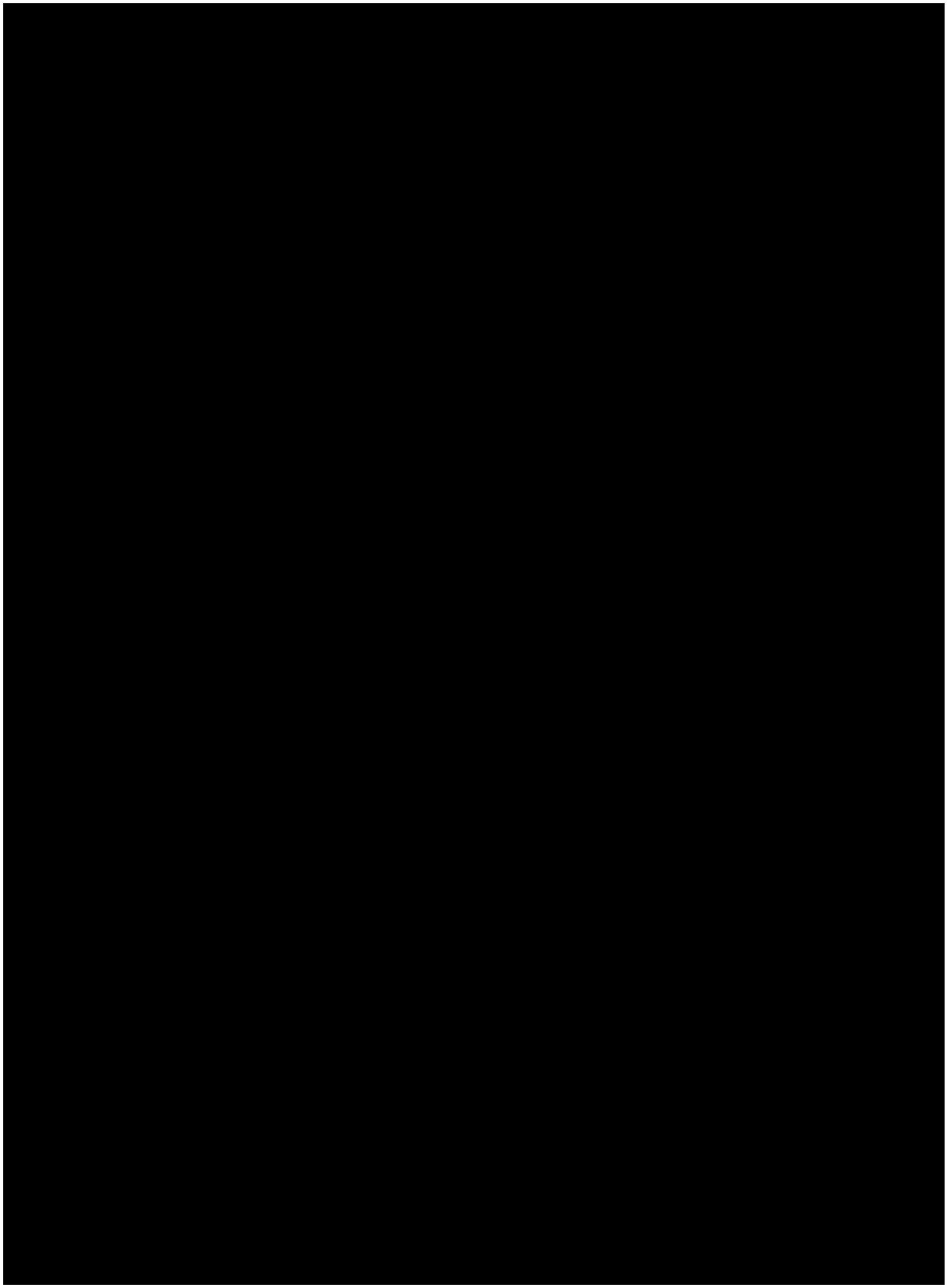
A listing of all ACEND (ACEND total score, total domain scores, subdomain scores, and item scores) will also be produced through the end of study.

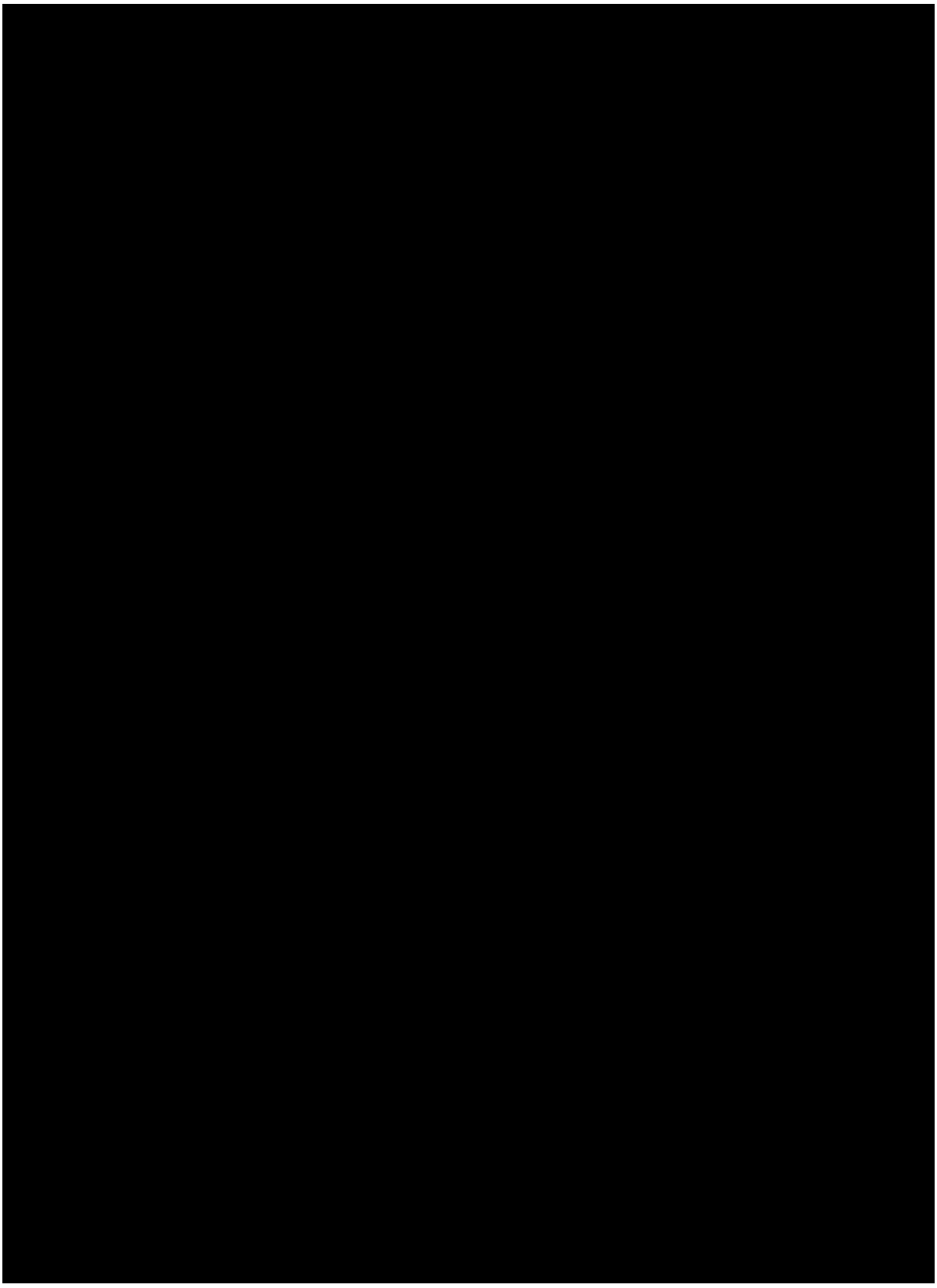


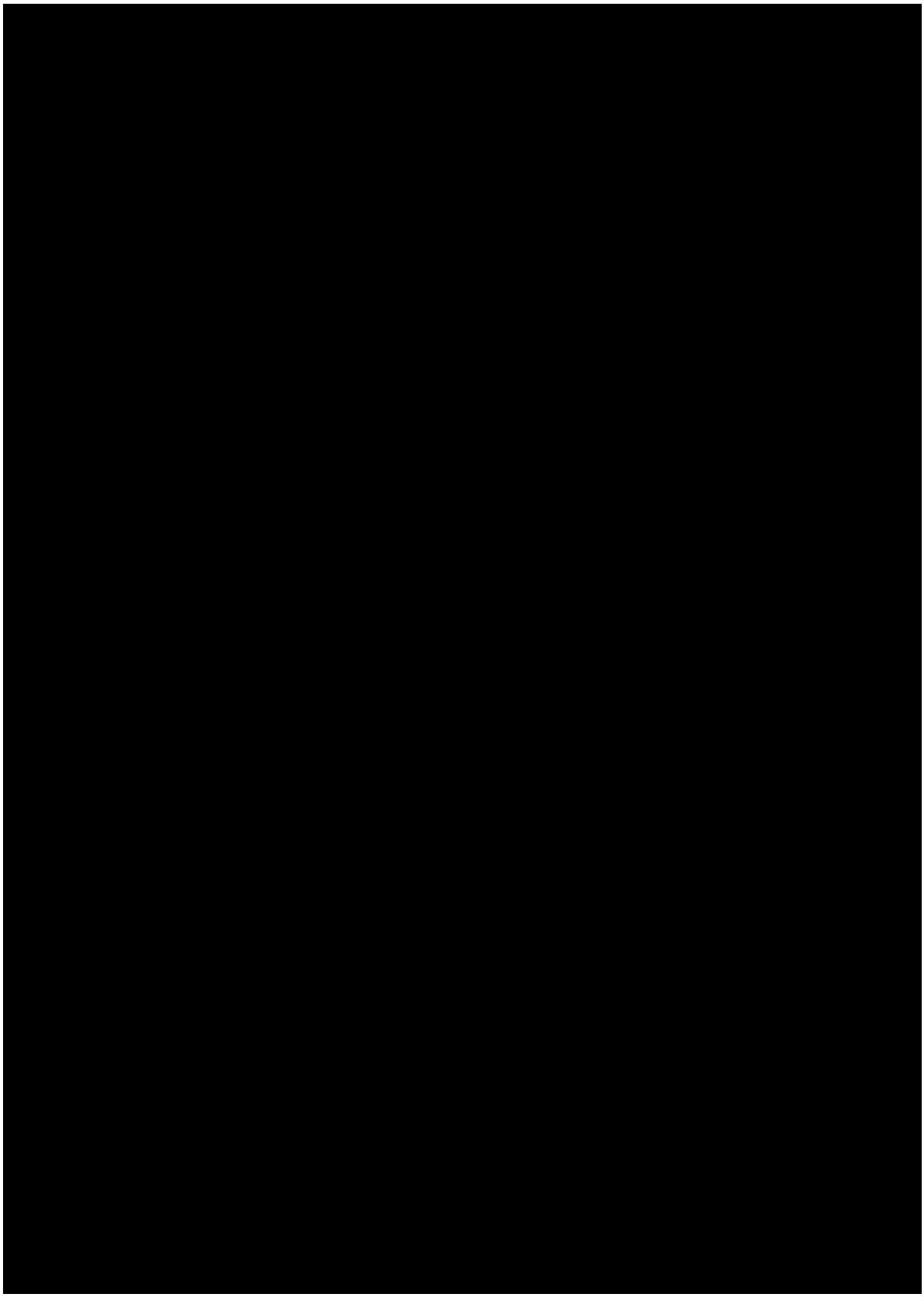


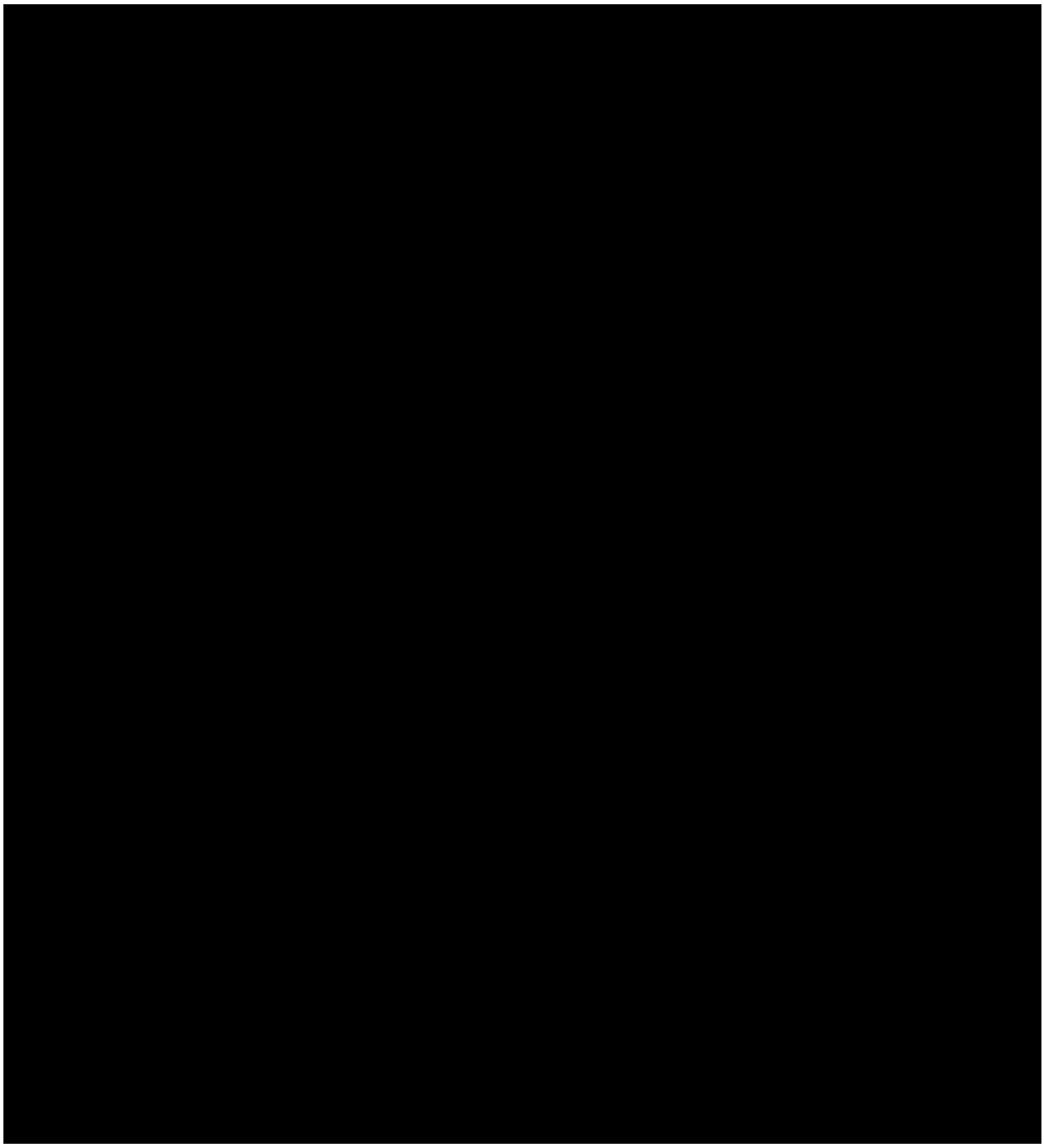












2.15 Interim analysis

Not applicable.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

Missing values for safety endpoints, including but not limited to AEs and laboratory values, will not be imputed.

5.1.1 Study drug

If the date of administration of investigational drug is missing or partial, it will be imputed as the date of the Day 1 visit.

5.1.2 Date imputation

Missing or incomplete AE start and/or end dates will be imputed according to the general Novartis imputation rules.

Missing or incomplete concomitant medication start and/or end dates will be imputed according to the general Novartis imputation rules.

5.2 AEs coding/grading

Verbatim terms of AEs, including important identified and important potential risks, will be encoded by means of MedDRA according to the data management plan.

5.3 Laboratory parameters derivations

Hy's law criteria apply (see Section 2.7.3).

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Not applicable.

5.4.2 Analysis supporting secondary objective(s)

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Analysis Set	Criteria that cause subjects to be excluded
FAS	Not enrolled in this study; Not having investigational treatment taken

5.6 Clinically significant vital sign values

Vital sign results will be flagged as clinically significant if they meet the pre-specified criteria which are defined as follows.

Systolic and Diastolic Blood Pressure:

- For participants aged <18 years at the time of assessment, diastolic and systolic blood pressure values greater than or equal to the corresponding to the 90th percentile value for age, gender, and height will be used to classify 'high' clinically significant values. The relevant values are contained in Table 4 (BP Levels for Boys by Age and Height Percentile) and Table 5 (BP Levels for Girls by Age and Height Percentile) of Flynn 2017.
    - Participants aged ≥2 to <3 years at the time of assessment will utilize the blood pressure levels defined for age 2 years, participants aged ≥3 to <4 years at the time of assessment will utilize the blood pressure levels defined for age 3 years, etc.
    - Height percentile will be defined using the height at the time of assessment, or the most recently recorded height prior to the assessment if the height at the time of assessment is not available. Participants with a height which falls between two percentiles will be classified according to the lower of the two percentiles. Participants with a height which falls below 5th percentile will be classified according to the 5th percentile. Participants with a height which falls above 95th percentile will be classified according to the 95th percentile.

- For participants aged 18 years and above at the time of assessment, systolic blood pressure values ≥120 mmHg and diastolic blood pressure values ≥80 mmHg will be classified as 'high' clinically significant values.
- For all participants regardless of age at assessment, systolic blood pressure values below the 5th percentile will be classified as 'low' clinically significant values. The 5th percentile value can be estimated using the following formula: 70 mmHg + (2*participant's age in years).

Temperature:

- For participants <18 years at the time of assessment, temperature values ≥38.4°C will be classified as 'high' clinically significant.
- For participants ≥18 years at the time of assessment, temperature values ≥39.1°C will be classified as 'high' clinically significant.
- For all participants regardless of age at assessment, temperature values ≤35°C will be classified as 'low' clinically significant.

Pulse rate:

The criteria for classifying high and low pulse rate values are contained in the table below (Flemming 2011).

Age at assessment	High (bpm)	Low (bpm)
2 to <3 years	>128	<92
3 to <4 years	>123	<86
4 to <6 years	>117	<81
6 to <8 years	>111	<74
8 to <12 years	>103	<67
12 to <15 years	>96	<62
15 to <18 years	>92	<58
≥18 years	≥120 with increase from updated baseline[1] of ≥15 bpm	≤50 with decrease from updated baseline[1] of ≥15 bpm

[1]Updated baseline is the last value collected before the participant's 18th birthday.

Weight:

- For participants <18 years at the time of assessment, weight values which reflect an increase from baseline of ≥2 BMI-for-age percentile categories (significant weight gain) will be classified as 'high' clinically significant; weight values which reflect a decrease from baseline of ≥2 BMI-for-age percentile categories (significant weight loss) will be classified as 'low' clinically significant.

  - Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to or greater than the 95th percentile).
  - BMI-for-age percentile are obtained from the WHO Growth Charts (https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age for 0 to under 5 years of age and https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age for 5 to 19 years of age, respectively).

- For participants ≥18 years at the time of assessment, weight values which reflect an increase from updated baseline of ≥10% will be classified as 'high' clinically significant and weight values which reflect a decrease from updated baseline of ≥10% will be classified as 'low' clinically significant. Updated baseline is the last value collected before the participant's 18th birthday.

Respiratory rate:

The criteria for classifying high and low respiratory rate values are contained in the table below (Flemming 2011; Eldridge 2014; Kou).

Age at assessment	High (breath/min)	Low (breath/min)
2 to <3 years	>34	<22
3 to <4 years	>29	<21
4 to <6 years	>27	<20
6 to <8 years	>24	<18
8 to <12 years	>22	<16
12 to <15 years	>21	<15
15 to <18 years	>20	<13
≥18 years	≥30	≤10

6 References

Eldridge L. What is a Normal Respiratory Rate?. Updated May 16, 2014.

FDA (2012) Guidance for industry. Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (last draft August 2012, available under http://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf)

Flemming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI: 10.1016/S0140-6736(10)62226-X.

Glanzman AM, O'Hagen JM, McDermott MP, et al (2011) Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol; 26(12):1499-507.

Kou R., Shuei L., Bradypnea, Department of Psychology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, http://rd.springer.com/referenceworkentry/10.1007%2F978-3-540-29676-8_246.

Matsumoto H, Clayton-Krasinski DA, Klinge SA, et al (2011) Development and initial validation of the assessment of caregiver experience with neuromuscular disease. J Pediatr Orthop; 31(3):284-92.

Mazzone ES, Mayhew A, Montes J, et al (2017) Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle Nerve; 55:869-74.

Mercuri E, Bertini E, Iannaccone ST (2012) Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol; 11:443-52.